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Ultrasound-mediated delivery of novel bio-responsive nanoparticles

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Nanotechnology has started a new era in biomaterial engineering and multifunctional nanoparticles (NPs) to improve diagnosis and therapy of various diseases, incorporating both contrast agents for imaging and drugs for therapy, has been designed.

Drug loaded nanoparticles (NPs) can improve the delivery of drugs to tumors and reduce toxic side-effects in normal tissue due to leaky blood vessels in tumor tissue, which do not exist in normal tissue. However, the blood vessel leakiness is heterogeneous in tumors, and NPs that can cross the capillary wall have problems penetrating the extracellular matrix around the cancer cells. Thus it is essential to enhance the delivery to all tumor tissue in order to improve the therapeutic outcome. Furthermore, new designs of NP based drug delivery system are needed to secure efficient drug release within tumors after accumulation of the NP drugs.

A challenge in cancer treatment is the delivery of drugs to brain tumors due the restriction of access to the brain that is strictly controlled by the blood-brain barrier (BBB). The endothelial cells forming the vessel wall are tightly linked together forming a physical barrier. Therefore, for inoperable diseases, non-invasive approaches for controlled transient opening of the BBB enabling the passage of therapeutics into the brain are highly needed.

Focused ultrasound has been shown both to improve the delivery of NPs to tumors (Eggen *et al.*, 2014) and to temporarily open the BBB (Åslund *et al.*, 2015).

A novel bio-responsive NP platform based on matrix metalloprotease (MMP) activatable liposomes will be used (Bruun *et al.*, 2015). MMPs are over-expressed in cancerous tissue and thus favorable for tumor targeting of nanoparticles for efficient drug release after tumor accumulation.

These NPs have already show promising results in preclinical studies and in the present project we aim at improving the delivery of these bio-responsive NPs to tumors and subcutaneous tumors by exposure to focused ultrasound in the presence of microbubbles. Improved delivery of NPs will be imaged by MRI, PET, small animal optical imaging and multiphoton microscopy. The therapeutic effect will be studied by measuring tumor growth.

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